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Review

Diagnosis of deep vein thrombosis, an overview

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Abstract

Because clinical signs and symptoms are unreliable the diagnosis of deep vein thrombosis (DVT) should be objectified. Advantages and disadvantages of contrast venography, plethysmography, ultrasound techniques, fibrinogen leg scanning, computer-assisted tomography, magnetic resonance imaging and blood tests are discussed. In patients with a first event of suspected DVT non-invasive methods like serial plethysmography or ultrasound testing are sensitive and specific enough to make a treatment decision. It is safe to withhold anticoagulants if the test remains normal within 1 week. In patients with suspected recurrent DVT new non-invasive techniques are being tested, but up to now the definitive objective diagnostic test continues to be contrast venography. In first period as well as in recurrent DVT D-Dimer testing could be an additional test to exclude active thromboembolism.

Keywords: Deep vein thrombosis; Venography; Plethysmography; Ultrasound; D-Dimer

1. Introduction

Venous thrombosis is a frequent clinical problem with considerable morbidity. The annual incidence of a first episode of clinically suspected venous thrombosis has been estimated at 2–4 per 1000 in the general population [1]. Prior to 1970 the diagnosis of deep venous thrombosis (DVT) was made on clinical grounds. With the introduction of contrast venography (CV) it became apparent that in only 30–60% of the patients with clinically suspected DVT the diagnosis is con-

firmed by venography [2–18]. This implies that for years patients with clinical signs of DVT were diagnosed incorrectly and challenged unnecessarily to the side-effects of anticoagulants with high costs of admission [19]. On the other hand, the diagnostic tests should be sensitive enough to prevent complications associated with pulmonary embolism (PE). Approximately 50% of patients with proven proximal vein thrombosis have evidence of silent PE on the pulmonary scintigram [20].

For a long time CV has been the reference method for the diagnosis of DVT [21]. The disadvantages of this procedure have led to the development of a wide array of less invasive tests like

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impedance-and strain-gauge plethysmography, Doppler ultrasound investigations, ultrasonography, duplex scanning, scintigraphic methods and blood tests to confirm or exclude venous thrombosis. In this paper the experience with these tests in two different situations is discussed: (1) patients showing signs and symptoms of DVT for the first time, (2) patients with previous DVT showing recurrence of signs and symptoms in the same limb.

2. Clinical signs and symptoms

In only 30–60% of patients with clinically suspected DVT the diagnosis is confirmed by CV [3,4,7,8,10–16,22–24]. The reason for the inaccuracy of the clinical diagnosis is that none of the signs and symptoms is unique and many other disorders can mimic DVT such as superficial phlebitis, trauma, postthrombotic syndrome, erysipelas, oedema due to congestive heart failure, external venous compression due to malignancy, burst Bakers' cyst, muscle tear, lymphangitis, lymphoedema and cellulitis.

Table 1 shows the positive predictive value of findings suggestive of DVT in different studies [4,12,13,15,25,26]. Remarkably the positive predictive value of the clinical signs seems better in the studies performed in the Netherlands [15,27]. Differences in patient categories (hospitalized

versus ambulant patients), the definition of clinical symptoms of DVT, difference in history taking and variety in referral patterns could explain the variability [27]. With an increasing number of positive signs the probability of DVT increases [12,15,27,28]. In our own hospital the positive predictive value of a combination of warmth, venous dilatation and increased circumference was 87%, as the frequency of this triad was 26% in our patients ($n = 141$) [unpublished observations].

In conclusion, major thrombosis can be present with minor symptoms and multiple signs of DVT do not necessarily mean thrombosis, necessitating objectivation of classical signs and symptoms by non-invasive testing or venography.

3. Contrast venography

The routine use of contrast venography (CV) in the diagnosis of DVT dates back to the early 1940's when understanding of the importance of venous thrombosis emerged [29]. It was by the use of this technique that the errors of the clinical examination were recognized. Currently it is still regarded as the gold standard for the assessment of the diagnosis of DVT [30]. If adequately performed, CV outlines the entire deep venous system of the leg, including the common iliac vein and inferior caval vein. In this way it establishes

Table 1

Positive predictive value of several "classical" signs of DVT, when the result of physical examination is compared to venography

	Haeger 1969 [4] (%)	Alexander 1974 [25] (%)	Richards 1976 [26] (%)	Lindqvist 1977 [13] (%)	Voorhoeve 1986 [15] (%)	Landefeld 1990 [12] (%)
Spontaneous pain	44			38	61	63
Palpatory pain	49	22	68			65
Increased circumference				40	63	61
Oedema	54	32	45	32	62	72
Warmth	50		71		68	32
Erythema		55		13	65	28
Homans' sign	58		72	15	62	21
Fever				17	68	59
Venous dilatation	60	79	75	17	93	

the presence, precise location, extent and occlusiveness of venous thrombi.

Of a number of methods for performing CV, ascending venography according to the technique of Rabinov [21] and Thomas [31] is most commonly used. Approximately 100 ml of low osmolar contrast medium is injected into a dorsal foot vein with the patient in a semi-erect position. In this position adequate filling of the leg veins occurs. Filling of the pelvic veins occurs when the X-ray table is tilted in a horizontal position. To establish a definite diagnosis of DVT views of the entire deep system from at least two directions are required. For this purpose separate films of the calf, knee, thigh and pelvic region are obtained.

Radiographic criteria for the presence of thrombosis have been defined previously [21]. The most reliable indicator of DVT is a constant intraluminal filling defect in at least two projections. Other, less reliable criteria are non-filling of a segment with abrupt termination and re-appearance of contrast media below and above the segment and non-filling of a vein of the deep venous system despite proper phlebographic technique. Whereas the observation of a constant filling defect is usually considered to represent acute venous thrombosis, the other findings may also result from old venous thrombi or artifacts.

CV may be used in first period DVT as well as in patients with recurrent signs of DVT, although the interpretation of a second venogram is often difficult because of anatomical changes in the venous system, vessel damage and resultant irregularities of the vessel wall by the former thrombosis [32].

Hull et al. demonstrated that of 160 patients with a negative venogram only 2 (1.3%) developed recurrent symptoms confirmed as DVT by impedance plethysmography and CV, and then only as a post-phlebographic thrombosis within 5 days of venography [33]. Recently in another follow-up study DVT occurred only in 1 patient out of 104 with a negative venogram [34].

Despite the diagnostic superiority of CV some disadvantages should be acknowledged. First, CV is an invasive procedure that may cause pain during the insertion of the needle and may pro-

duce pain in the foot or calf while the contrast material is injected. In the past, contrast-media-related complications have been described such as "the phlebographic syndrome" (pain, warmth, erythema and swelling of ankle and distal calf), phlebitis, DVT and allergic reactions [35–37]. Since the introduction of low-osmolar contrast materials these complications are much less frequent. Recently it was demonstrated that the use of low osmolar non-ionic contrast material is associated with minor side-effects in approximately one fifth of patients and that serious adverse reactions, necessitating therapy, are rare (0.4%) [38].

The second limitation of CV is related to the sometimes difficult technique and interobserver disagreement in interpretation of the venograms [30,39,40]. Lensing et al. compared the Rabinov technique [21] with the long-leg method: the injection of a larger volume of contrast medium and the concomitant use of long films instead of spot films. They concluded that the long-leg method is superior, since it significantly improved interobserver agreement (from 79 to 96%) and increased the number of interpretable venograms (from 80 to 98%) [30].

Finally, CV cannot be performed in up to 10% of patients because of inability to acquire venous access, a history of allergic reactions to contrast materials, a local infection of the leg or renal insufficiency [31].

In our own hospital out of 257 planned venograms only 5 (1.9%) could not be performed, in another 2% there were difficulties in interpretation while no allergic reactions or thrombophlebitis occurred. Fifty patients were retrospectively interviewed about side-effects: 20% experienced it as unpleasant.

The minor disadvantages have led to a search for replacement or supplementation by non-invasive tests [24].

4. Non-invasive tests

Plethysmography

Plethysmography is one of the most widely used non-invasive techniques. The method is

based on measurements of changes in blood volume in the leg produced by temporary venous obstruction. During a period of venous outflow occlusion by a thigh cuff the increase in volume is measured. Following maximal filling of the leg the venous outflow is measured after termination of the venous occlusion. An obstruction in venous outflow like proximal DVT causes a decrease in maximal venous outflow. The methods currently used are impedance plethysmography and strain-gauge plethysmography.

Impedance plethysmography (IPG)

IPG is based on the principle that blood volume changes in the leg lead to changes in electrical resistance (impedance) [41].

Accuracy studies in patients with a proximal DVT using CV as the reference method have shown an overall mean sensitivity of 94% (range 87–100%) and specificity of 95% (range 91–100%) in first episode DVT (Table 2). Consequently an abnormal test result justifies the initiation of anticoagulant treatment. Its sensitivity in calf vein thrombosis is considerably less (20%) because venous outflow may be possible through other patent calf veins; its specificity remains high at about 95% [16,42–49].

A number of studies have evaluated the use of serial IPG in patients with a first episode of signs and symptoms suggesting DVT [50–54]. The use of this serial IPG is based on the fact that 20% of calf vein thromboses extend and assumes the

Table 2
Comparison of impedance plethysmography, strain-gauge plethysmography, ultrasonography, Doppler with contrast venography as the gold standard in the diagnosis of proximal DVT

Author	No.	Prevalence (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
<i>Impedance plethysmography</i>						
Hull 1976 [42]	618 *	25	93	97	92	98
Toy 1978 [43]	30	52	94	100	100	90
Cooperman 1979 [47]	98	34	87	96	89	96
Hull 1981 [48]	293	42	95	95	93	93
Peters 1982 [49]	185	33	92	93	85	92
Anderson 1993 [59]	142	39	66	76	65	77
<i>Strain-gauge plethysmography</i>						
Barnes 1977 [60]	387 *	35	90	81	59	94
Bounameaux 1982 [64] ^o	87	56	91	63	75	85
Klein Rouweler 1989 [67]	76	54	95	100	100	95
Laverick 1992 [63]	171	30	95	80	46	99
Croal 1993 [62]	274 *	34	100	66	37	100
<i>Ultrasonography</i>						
Dauzat 1986 [71]	145	69	94	100	100	88
Appelman 1987 [73]	121	56	96	97	96	97
Cronan 1987 [74]	51	55	89	100	100	88
Lensing 1989 [68]	220	35	100	99	99	100
Cogo 1993 [78] [∞]	158	35	100	100	100	100
<i>Doppler</i>						
Bounameaux 1982 [64] ^o	87	49	84	75	84	75
Sandler 1984 [2]	50	58	75	89	72	90
Voorhoeve 1986 [15]	164	62	94	90	94	77
Lensing 1990 [92]	110	45	91	99	98	96
Cogo 1993 [78] [∞]	158	35	89	98	96	95

PPV = positive predictive value; NPV = negative predictive value.
*n = limbs instead of patients; ^o/[∞] from the same study.

hypothesis that calf-vein thrombi that are undetected by repeated IPG during a 10-day period, thus without proximal extension, are not clinically relevant and thus should not be treated with anticoagulants. This is based on the observation that the frequency of recurrent venous thromboembolism in studies using serial IPG during the 6-month study period was very low (0.3–1.9%), which is not higher than the figures obtained in a follow-up study in symptomatic patients with a normal venogram [33].

IPG can also be used to diagnose recurrent DVT in some cases [32]. It was demonstrated that normalisation of IPG occurs in almost all patients within 9 months. To make this approach clinically useful, patients with documented DVT should undergo follow-up IPG at the end of the anticoagulant therapy, usually after 3–6 months, until the IPG becomes normal. The utility of this approach was confirmed by long-term follow-up [55–57].

The accuracy of different IPG machines is not equal. Recently a newly developed computerized IPG (CIPG) has become available which has the advantages of easy portability and a simplified test procedure. Unfortunately, the study to test CIPG was prematurely terminated because of an unacceptably high incidence (3.2%) of missed DVT as confirmed by CV [58]. Anderson et al. re-evaluated the accuracy of an IPG machine and found a sensitivity of only 66% for proximal vein thrombosis [59]. This shows the necessity both for a prospective validation of any new equipment with CV as the reference method and for a subsequent management study.

Strain-gauge plethysmography (SGP)

SGP detects volume changes in the limb by measuring circumferential changes in the part of the limb around which the strain gauges are placed. Stretching of the strain gauge causes a change in electrical resistance, proportional to the amount of stretching. SGP has not been as extensively evaluated as IPG, but because the principle is very similar some researchers translate IPG findings into SGP findings. Whether this is justified is still unknown. The reported sensitivity and specificity range from 95–100% and 80–

100%, respectively (Table 2). Like IPG, SGP is sensitive and specific in proximal vein thrombosis, but lacks accuracy in calf vein thrombosis [60–67].

Ultrasonography

B-mode ultrasonography (US) is a non-invasive diagnostic imaging technique that has acquired widespread clinical application, particularly with the development of real-time techniques. The technique is based on the concept that ultrasound traversing biologic structures are reflected from barriers (interfaces) between structures with different acoustic impedances. US is carried out with a 5–10 MHz high-resolution transducer. By recording the amplitudes of the returning echoes and displaying them on a screen, a two-dimensional anatomic image of the structures being studied is obtained.

The potential advantages of this method are that the technique is non-invasive, easy to perform, widely available in many hospitals and allows direct visualization of the thrombus.

The most accurate and simple criterion for the presence of DVT is non-compressibility of the vein under gentle probe pressure (compression US) [68]. Further diagnostic criteria comprise visualization of the thrombus and the absence of vein extension upon a Valsava manoeuvre. Most of the ultrasound accuracy studies limit the examination to compressibility of the common femoral vein and the popliteal vein. Visualization of the thrombus may be difficult and is not always reproducible. By reviewing 189 venograms Cogo et al. proved that it is safe to limit compression US examination of the proximal veins to the common femoral and popliteal vein, so an abnormal two-point US result can be used to make therapeutic decisions [69].

Numerous studies comparing US with CV have shown a consistently high sensitivity (97%) and specificity (97%) of US for proximal thrombosis [22,68,70–79]. Table 2 shows a selection of these studies. There are two potential disadvantages of US. First the sensitivity for calf vein thrombosis is low, because of the small size and anatomic variation of these vessels. Second, isolated thrombi in the iliac vein and in the superficial femoral vein within the adductor canal are difficult to detect.

Effeney et al. developed a method to detect isolated iliac vein thrombosis by measuring the increase of the common femoral vein diameter while performing a Valsalva manoeuvre. The increase in diameter was less than 50% in the case of iliac vein thrombosis [80].

A limited number of studies have evaluated the clinical of US validity in the management of patients with symptomatic venous thrombosis with US performed serially [81–83]. Although normal US excludes proximal vein thrombosis, isolated calf vein thrombosis may be present and proximal extension may develop. Hence, only in patients with serial normal US is no anticoagulant treatment indicated. The approach to withhold anticoagulant therapy in symptomatic patients with serial normal US and serial normal IPG results proved to be safe [54]. Such a second US examination is only indicated if clinical symptoms persist.

The usefulness of US in the diagnosis of recurrent DVT has been questioned, because normalisation occurs in only 55–73% during the first year [84–86]. These values are in contradiction to the values obtained by IPG; normalisation of IPG occurred in almost all patients within 9 months [56]. For this reason the use of the criterion of compression is of limited value for recurrent DVT diagnostic management. To overcome this problem Prandoni et al. developed a simple ultrasound method for measuring thrombus regression and showed that serial US measurement of thrombotic mass diameter after an acute DVT allows the correct identification of patients who develop a recurrent proximal vein thrombosis (sensitivity and specificity for proximal DVT of 100%) [87]. Validation of this method with CV is necessary and management studies are needed to determine if it is safe to make therapeutic decisions on the outcome of the test.

Continuous-wave Doppler

Continuous-wave Doppler systems (Doppler) utilize a probe with an emitting and a receiving piëzo-electric crystal. One crystal transmits an ultrasound beam with a transmission frequency of 5–10 MHz. The other crystal receives the back-scattered sound waves. Erythrocyte velocity is calculated using the Doppler shift principle.

Criteria associated with DVT are respectively absence of flow, continuous flow without phasicity with respiration, and absence or diminished augmentation of flow with distal compression or proximal decompression.

The value of Doppler in the diagnosis of DVT has been evaluated in several prospective studies with venographic control [2,15,18,22,64,78,88–93]. The results for proximal DVT are presented in Table 2. The reported sensitivity and specificity show a wide range, partly due to the subjective nature of the technique. The introduction of a standardized protocol has improved its accuracy [92], although it is still suggested that US is superior to Doppler in the detection of DVT in symptomatic outpatients [78].

Studies on the safety of withholding anticoagulant therapy in patients with normal Doppler examinations are lacking. The value of Doppler in patients with recurrent DVT has hardly been evaluated.

(Colour) Duplex scanning

Duplex scanning is the combination of pulsed Doppler systems with two-dimensional B-mode imaging. The diagnosis of DVT is based on a combination of criteria mentioned earlier (visualization of thrombus, abnormal vessel wall compressibility or abnormal venous flow signals).

The accuracy of duplex scanning in the diagnosis of proximal DVT is comparable to US imaging. The overall sensitivity is 93% (range 87–100%) and the overall specificity is 94% (range 78–100%) [94–98]. In a recent study it was shown that US and duplex are methods with comparable high accuracy. Because of its availability, accuracy, cost-effectiveness and simplicity US was recommended as the primary diagnostic test [99].

¹²⁵I-Fibrinogen scanning (IFS)

From several scintigraphic methods developed to detect DVT only IFS has been thoroughly evaluated and introduced in clinical practice [72,100–103]. The diagnosis of venous thrombosis by IFS is based on incorporation of circulating labelled fibrinogen into the thrombus, which is then detected by measuring increase of overlying surface radioactivity with an isotope detector.

IFS is relatively insensitive in the upper thigh and pelvic area, because of the high background radioactivity in the bladder. False positive results may be caused by conditions leading to an accumulation of fibrinogen, such as haematoma, oedema, inflammatory reactions, incisions, arthritis, ulceration and bone fractures. A false negative scan may occur with an older venous thrombus which no longer incorporates fibrinogen, when the thrombus is too small to be detected by leg scanning, or when the thrombus is isolated in the common femoral or iliac vein [104,105]. IFS was subsequently used in the diagnosis of asymptomatic DVT in high-risk patients and was the most commonly used method for assessing the effect of prophylactic regimens [106,107].

Initial studies showed a high sensitivity for calf DVT (90%), but in later studies its sensitivity was much lower (55%) [104,105,108]. According to a recent review of the literature the high sensitivity of the initial studies was due to bias; the two diagnostic tests were not interpreted independently [109]. There is also evidence that the sensitivity of leg scanning is influenced by the size and location of the thrombus, being higher in large thrombi and in thrombosis located in the calf [104].

Another limitation of this technique is the need for radioactive fibrinogen, with its associated risk for virus transmission as fibrinogen is derived from human plasma and cannot be pasteurized. Finally this technique is invasive, while there are ethical and logistic problems of radioactive tests.

Computer-assisted tomography and magnetic resonance imaging

Computer-assisted tomography is considered superior to CV in visualizing the major veins, identifying intraluminal thrombi and distinguishing adjacent abnormalities [110]. Magnetic resonance imaging of lower and pelvic veins has only been evaluated in small clinical trials: a sensitivity of 100% and a specificity of 96% was reported for the diagnosis of DVT [111–113]. Because of the high costs and limited availability, these techniques are now only used in exceptional cases but need further evaluation [114].

5. Blood tests

In the past decade plasma assays of several markers of activation of plasma coagulation and fibrinolysis have become clinically available: FDP (Fibrinogen Degradation Products), Fibrinopeptide A, D-Dimer (degeneration products of cross-linked fibrin), F 1 + 2 (prothrombin fragments) and TAT (thrombin–antithrombin III) complexes. Of these markers D-Dimer (DD) has been studied most extensively as a potential aid in the diagnostic management of DVT. Table 3 gives a summary of studies in which plasma measurements of DD (ELISA) were performed in the diagnosis of DVT [115–121]. The results of these investigations show that a low concentration of plasma DD measured by the ELISA technique might be used to rule out venous thrombosis in clinically suspected patients: its sensitivity is 92–

Table 3
Summary of studies in which plasma measurements of D-Dimer (ELISA) were performed in the diagnosis of DVT

Author	No.	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Cut-off value (ng/ml)
Heaton 1987 [115]	57	100	47	62	100	400
Rowbotham 1987 [116]	104	100	34	54	100	500
Ott 1988 [117]	108	97	65	61	98	400
Bounameaux 1989 [118]	53	95	47	54	94	500
Boneu 1991 [119]	116	98	29	53	94	500
Heyboer 1992 [120]	309	100	29	29	100	300
Hansson 1994 [121]	105	94	60	66	92	200

PPV = positive predictive value; NPV = negative predictive value.

100%. Because of the low specificity of this test increased plasma concentrations are of no value [115–125].

The sensitivity of the latex DD-test is lower compared with the ELISA technique [115,118,126]. However, another recent study showed a similar sensitivity for both [121]. Another possibility is to use a latex assay (which is performed more quickly and is cheaper) as a first diagnostic step to rule out DVT provided a negative result is confirmed by ELISA [124].

In conclusion, DD-testing cannot be used as the only diagnostic tool to detect thrombosis because of its low specificity. However, it could be a valuable additional test to exclude thrombo in the

first period of suspected DVT as well as in recurrent signs of DVT. Further research, such as management studies in patients clinically suspected of DVT, has to be performed [127]. Also, more rapid DD tests (more sensitive latex assays or more rapid ELISA's) have to be developed [128].

6. Summary

Because the clinical diagnosis of DVT is unreliable, additional diagnostic techniques are needed. CV is accurate, but has some disadvantages. Several non-invasive techniques were dis-

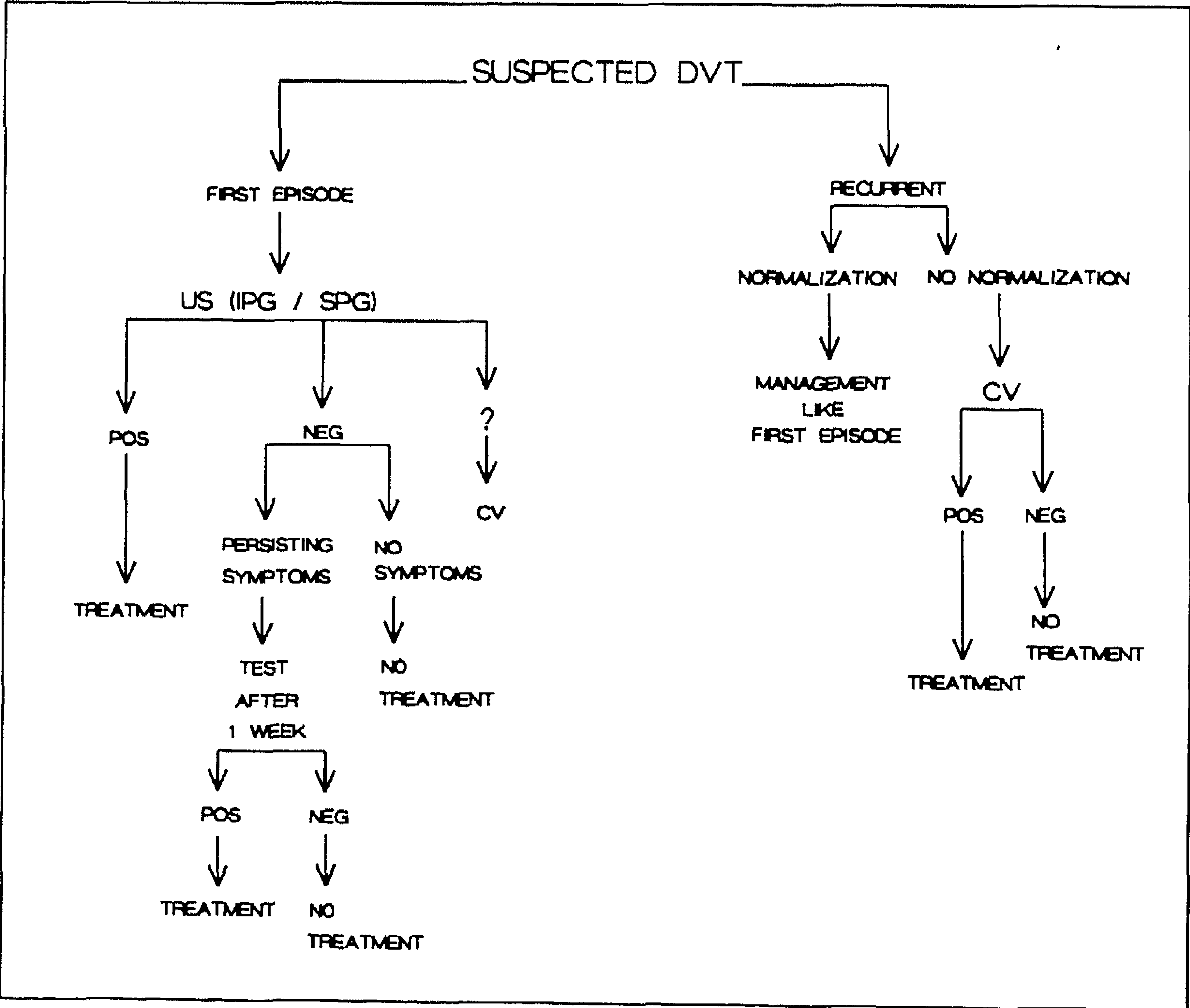


Fig. 1. Diagnostic approaches to suspected deep venous thrombosis. US = ultrasound; IPG = impedance plethysmography; SGP = strain gauge plethysmography; CV = contrast venography.

cussed in the diagnosis of DVT in two different categories: (1) patients with a first period of suspected DVT and (2) suspected recurrent DVT. The approaches are summarized in Fig. 1.

In patients with a first event of suspected DVT non-invasive methods are most suitable. Of these methods IPG and US have been the most thoroughly evaluated and have proved to be safe and effective. An abnormal test justifies the initiation of anticoagulant therapy, but a negative result does not exclude distal DVT. If clinical symptoms persist, serial testing is indicated to detect extending calf vein thrombosis; it is safe to withhold anticoagulant therapy if the test remains normal within 1 week. US has several advantages over IPG and SGP: its sensitivity is higher, it is cheaper, more widely available and easier to perform in inpatients. If these two methods are not available, if there is no set-up for serial testing or if the test results are difficult to interpret, CV should be performed.

Because IPG, SGP and US are operator-dependent, its introduction as a new method in any hospital should be preceded by a transitional phase with combined CV to check whether the local predictive values are close to the data in the literature.

In patients with suspected recurrent DVT non-invasive tests are only useful when the test became normal during the follow-up of the first DVT: if the test has changed in an abnormal manner it is justified to start anticoagulants. In the case of incomplete normalisation newly developed quantitative measurements seem to be promising, but await further confirmation. CV should not yet be replaced in the diagnosis of recurrent DVT until more studies are performed.

In suspected first-period DVT as well as in recurrent DVT, detection of D-Dimer could be an additional test to exclude active thrombosis. Because of its low specificity it cannot be used as the only diagnostic tool.

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